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Filed : February 12, 2002

REMARKS

Applicants acknowledge receipt of the Office Action mailed April 25, 2005. Claims 1-16 are pending. Claim 1 has been amended to correct a minor typographical error. Claim 8 has also been amended. Support for the amendment to Claim 8 can be found in the original claims as filed and throughout the specification. Support can be found at, for example, paragraph [0029], [0046], and [0047] of the specification. Claim 10 has been canceled. Claims 8-16 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Claims 8-11 were also rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,626,883 (the '883 patent). Claims 1-7 and 8-14 were rejected under 35 U.S.C. §103(a) as being obvious in view of the cited art. Claims 1-9 and 11-16 are pending and presented for examination.

Claims 8-16 are fully enabled by the specification under 35 U.S.C. §112, ¶ 1

Claims 8-16 were rejected under 35 U.S.C. §112, first paragraph. 35 U.S.C. §112, first paragraph requires that the specification provide a written description of the invention. According to the PTO, the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Specifically, the PTO objected to the phrase "wherein said NK cell activating cytokine is not IL-2" as allegedly lacking support in the specification. Applicants respectfully disagree.

It is well-settled law that if alternative elements are positively recited, they may be explicitly excluded in the claims. *See In re Johnson*, 558 F.2d 1008, 1019 (CCPA, 1977) (holding that the specification, having described the whole, necessarily described the part remaining). *See, also* M.P.E.P. § 2174.05(i). Here, the specification describes IL-2 as well as a number of alternative NK cell activating cytokines including, for example, IL-1, IL-12, and IFN- γ . In paragraph [0035], for example, dosage ranges of IL-1, IL-2, and IL-12 for use in treating neoplastic disease are described. Because IL-2 and other alternative NK-cell activating cytokines are positively recited in the specification, Applicants are entitled to explicitly exclude IL-2 from the claims pursuant to § 2174.05(i) of the M.P.E.P. Therefore, Applicants respectfully request withdrawal of the rejection of Claims 8-16 under 35 U.S.C. §112, first paragraph.

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Claims 8-11 are not anticipated under 35 U.S.C. §102(e) by U.S. Patent No. 5,626,883

Claims 8-11 were rejected under 35 U.S.C. §102(e) as being anticipated by the '883 patent. The '883 patent teaches ascorbate preparations that includes flavonoids such as hesperidin, rutin, quercetin, proanthocyanidine, flavonols, and methoxyflavonols for treating cancer by activating NK cells. Claim 8 has been amended to clarify specific hydrogen peroxide scavengers, which exclude ascorbate. Under 35 U.S.C. § 102(e), a claim is anticipated only if the reference teaches each and every limitation of the claim. M.P.E.P. § 2131. Applicants assert that each element as set forth in Independent Claim 8, as amended, and the claims depending therefrom, are not found in the '883 patent. The '883 patent teaches the administration of ascorbic acid and flavonoids to activate NK-cells. Claim 8, as amended, is limited to hydrogen peroxide scavengers that include catalase and glutathione peroxidase. Because the '883 patent is limited to the use of ascorbic acid with flavanoids and does not teach or suggest the presently claimed hydrogen peroxide scavengers, the reference fails to teach each and every limitation of the claims. Accordingly, Applicants respectfully submit that the claims are not anticipated by the '883 patent and request withdrawal of the PTO's rejection under 35 U.S.C. §102(e).

Claims 1-7 is not obvious under 35 U.S.C. §103(a) over U.S. Patent No. 4,588,585 in view of Hellstrand et al.

Claims 1-7 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 4,588,585 (the '585 patent) in view of Hellstrand et al. *Cellular Immunology* 138: 44-54 (the "Hellstrand" reference). According to the PTO, it would have been obvious to one of skill in the art to combine IFN- β mutein as taught in the '585 patent with histamine as taught by the Hellstrand reference for the treatment of tumors as is presently claimed. To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants assert that the PTO has failed to establish a *prima facie* case of obviousness.

The '585 patent describes a synthetic mutein of IFN- β and IL-2. These mutationally altered biologically active proteins were reported to have activity in stimulating NK cells and

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may be useful in treating neoplasia. However, the '585 patent does not teach the administration of an NK cell-activating cytokine with histamine, other H₂ receptor agonists, or serotonin. Hellstrand et al. reports that histamine reversed the monocyte-induced down modulation of NK cells. According to the PTO, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the IFN- β mutein of the '585 patent with histamine as taught by Hellstrand, since the cited art teach that both are useful for augmenting NK cell anti-tumor cell cytotoxicity.

Applicants submit that it would not have been obvious to combine the reference teachings. This is because there must be some teaching, suggestion, or incentive to make the combination in the prior art. See, e.g. *In re Fine*, 5 U.S.P.Q. 1272 (Fed. Cir., 1988). No such teaching, suggestion, or incentive is provided by any of the references of record in this case. Moreover, neither of the references, alone or in combination, suggests modification of the reference teachings to arrive at the presently claimed invention. Finally, the cited references provide no reasonable expectation of success in achieving the claimed invention. Accordingly, the present claims are non-obvious under 35 U.S.C. §103(a).

The cited art does not provide a suggestion of using a NK cell stimulator and a compound that inhibits the production of or scavenges hydrogen peroxide to stimulate NK cell cytotoxicity. Rather, the '585 patent merely teaches that a synthetic IFN- β or IL-2 mutein has the ability to augment NK cell function. There is no mention in the reference that NK cells activated by these various agents will be down-regulated in the presence of monocytes. Further, there is no suggestion that monocytes produce hydrogen peroxide as a mechanism for down regulating NK cells. Moreover, the reference is silent as to the potential for administering peroxide scavengers or inhibitors to potentiate the anti-tumor effects of NK cell activators in the presence of monocytes.

The PTO has cited Hellstrand *et al.* as a basis for finding the claims obvious under 35 U.S.C. §103. Hellstrand et al. describe a mechanism by which histamine may mediate the down regulation of NK-cells. However, the reference does not teach the administration of cytokines with a compound that inhibits the production or release of hydrogen peroxide or scavenges hydrogen peroxide to stimulate NK cell activity. Moreover, the reference neither describes nor suggests the greater than additive effects of the administration of an NK-cell activating

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compound with histamine or histamine-like compounds as is reported in the present application. Because of these deficiencies, the Hellstrand reference does not, either alone, or in combination with the '585 patent discussed above, render the pending claims obvious.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000). Applicants submit that the PTO has pointed to no motivation to modify the reference teachings to arrive at the claimed method of inhibiting tumor growth by administering an NK cell activating cytokine or flavonoid with a compound effective to inhibit the production or release of hydrogen peroxide. Neither the '585 patent nor the Hellstrand reference describe any benefits the administration of a NK cell activating cytokine or flavonoid with a compound effective to inhibit the production or release of hydrogen peroxide might evince in inhibiting tumor growth. Moreover, neither reference describes, suggests, or appreciates the synergistic effect the co-administration of these compounds would have on inhibiting tumor growth.

Absent Applicants' present disclosure, there is no suggestion or motivation in the prior art to combine a NK-cell activating cytokine or flavonoid with a compound that inhibits the production or release of hydrogen peroxide or scavenges hydrogen peroxide. The mere fact that the reference teachings might be modified or combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); See, also M.P.E.P. §2143.01. In *In re Fine*, the Federal Circuit made clear that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Instead, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the art would make the combination and that knowledge cannot come from the applicant's disclosed invention. See *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992)(emphasis added). Absent impermissible hindsight, it would not have been obvious to administer a NK cell activating cytokine or flavonoid with histamine, other H₂ receptor agonists, or serotonin as is presently claimed.

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Even if a *prima facie* showing of obviousness were established, the unexpected synergy that results from the combination of the NK cell activator and the hydrogen peroxide scavenger or inhibitor would clearly rebut such a showing. The data included in the specification demonstrate that the combination of an NK cell activating compound and a peroxide scavenger or inhibiting compound administered in the presence of monocytes not only prevents the inactivation of NK cells but also enhances NK cell cytotoxicity against tumor cells. These are unexpectedly superior results, since under similar circumstances, NK cell activators alone since under similar circumstances, NK cell activators alone had no such beneficial effect (See, e.g. Examples 1 and 2 of the specification).

Applicants have demonstrated that the cited references fail to provide the necessary teaching, motivation, or suggestion to create a *prima facie* showing of obviousness. Moreover, even if there were a *prima facie* showing of obviousness, such a showing would be rebutted by the significant unexpected synergy provided by the claimed invention. Accordingly, Applicants respectfully request withdrawal of the Examiner's rejections under 35 U.S.C. §103.

Claims 8-14 are not obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 4,588,585 in view of U.S. Patent No. 5,626,883

Claims 8-14 were rejected under 35 U.S.C. § 102(a) as being unpatentable over Mark (U.S. Patent No. 4,588,585, the '585 patent) in view of Paul (U.S. Patent No. 5,626,883, the '883 patent). According to the PTO, the '585 patent teaches a method of treating neoplasia by administering IFN- β mutein, and that the administration of IFN- β mutein is effective to activate NK cells. However, the '585 patent is silent with regard to the combination of IFN- β mutein with a hydrogen peroxide scavenger. The PTO further asserts that '883 patent teaches methods of administering vitamin C supplements comprising ascorbate to enhance NK cell activity and to treat cancer. Thus, according to the PTO, it would have been obvious to a skilled artisan to combine the IFN- β mutein disclosed in the '585 patent with the vitamin C preparation as taught in the '883 patent to arrive at the claimed invention, since both compounds are useful for the treatment of tumors and for the augmentation of NK cell anti-tumor cell cytotoxicity. Applicants disagree.

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It would not have been obvious to combine the teachings of a synthetic NK cell activator as taught in the '585 patent with the teachings that a hydrogen peroxide scavenger can augment the cytotoxicity of NK cells as taught in the '883 patent. This is because there must be some teaching, suggestion, or motivation to make the combination made by the inventor. See, In re Fine. However, neither of the cited references teach or suggest the mechanism by which down-regulated NK cell activity can be restored. Without an understanding of the mechanism by which NK cells are down regulated by the presence of hydrogen peroxide produced by monocytes, one of ordinary skill in the art would have no motivation to combine an NK cell stimulator with a hydrogen peroxide scavenger to potentiate NK cell cytotoxicity. Moreover, the '883 patent neither teaches nor suggests that other compounds that scavenge or inhibit the production or hydrogen peroxide would have any effect on NK cell activity.

Hence, there is no suggestion or motivation provided by the references to combine a hydrogen peroxide scavenger with an NK cell activator to eliminate the inhibitory effect of hydrogen peroxide produced by monocytes. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicants' disclosure. *In re Dow Chemical*, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Thus, no *prima facie* showing of obviousness is provided by the prior art of record.

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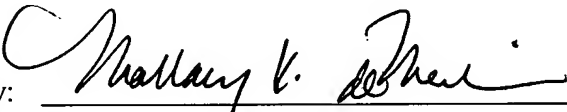
CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims. The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain, or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Respectfully submitted,

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